The Egyptian Journal of Hospital Medicine (October 2023) Vol. 93, Page 7002-7008

Thyroid Disorders in Juvenile Idiopathic Arthritis Patients and Its Correlation with Disease Activity: A Cross-Sectional Study

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ABSTRACT

Background: The association between juvenile idiopathic arthritis (JIA) and thyroid disorders has been defined in adults and, less frequently, in children.

Objective: The study's goal was to assess thyroid function and the prevalence of thyroid antibodies in patients with juvenile idiopathic arthritis, as well as their relationship to disease activity.

Methods: This cross-sectional study included 50 children and adolescents with juvenile idiopathic arthritis. All patients underwent thyroid function tests (thyroid stimulating hormone, free thyroxine, and free triiodothyronine), anti-thyroglobulin and anti-peroxidase antibodies by enzyme-linked immunosorbent assays.

Results: The study showed that 52% of the patients were males and 48% were females. Their median age value was 9 years old. Thyroid abnormalities were detected in 52% of JIA patients. Overt hypothyroidism was the most prevalent disorder [14 patients (28%)], followed by subclinical hypothyroidism [11 patients (22%)], and then subclinical hyperthyroidism [1 patient (2%)], while 24 patients (48%) were euthyroid. Thyroid antibodies showed a normal level in all patients. On comparing thyroid function tests among patients with active and inactive JIA, no statistically significant difference was observed in thyroid hormone levels.

Conclusion: To reduce the risk of delayed or undiagnosed thyroid diseases, it is necessary to routinely screen for thyroid function abnormalities in children with juvenile idiopathic arthritis.

Keywords: Juvenile idiopathic arthritis, Thyroid autoantibodies, Thyroid function, Hypothyroidism.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most prevalent chronic rheumatic illness in children and can trigger chronic pain, joint injury, and disability [1]. It is defined as an autoimmune inflammatory arthritis that develops in children less than 16 years old, persists over 6 weeks, and is of unknown aetiology [2].

The existence of other autoimmune diseases in children with JIA has been reported, and thyroid dysfunction is the most frequently involved [3]. Subclinical hyperthyroidism, subclinical hypothyroidism, hyperthyroidism, and hypothyroidism are the main forms of thyroid dysfunction. The most frequent cause of different thyroid dysfunctions is autoimmune thyroid disease (AITD), which includes Graves' disease and Hashimoto's thyroiditis, as revealed by the generation of antithyroid antibodies [4].

The presence of autoimmune disorders that co-exist in JIA patients can be explained by the generalized dysregulation of the immune system in those patients, which have been described to decrease life quality and increase the risk of disability and mortality [5].

There are limited studies assessing thyroid function and estimating the prevalence of other autoimmune conditions, including autoimmune thyroid disease, in children and adolescents with JIA [6, 7]. This study was done to evaluate thyroid function, and the prevalence of thyroid antibodies in juvenile rheumatoid arthritis patients, and their association with disease activity.

MATERIAL AND METHODS

Study design and data collection: This cross-sectional study included 50 children and adolescents with juvenile idiopathic arthritis (JIA) who attended at regular intervals for follow-up at the Rheumatology Unit of Specialized Pediatrics Hospital. Cases were recruited from March 2019 to June 2019.

Inclusion criteria: Patients less than 16 years old of both genders diagnosed with JIA according to the International League of Associations for Rheumatology's (ILAR) classification of juvenile idiopathic arthritis subtypes (JIA include 7 subtypes: systemic arthritis, oligoarthritis, polyarthritis rheumatoid factor positive, polyarthritis rheumatoid factor negative, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis) [8].

Exclusion criteria:

Patients with thyroid abnormalities caused by other conditions or taking medications that can impair thyroid function, as well as those with other rheumatological diseases.

Clinical manifestations of the disease, such as fever and arthritis along with a high erythrocyte sedimentation

Received: 28/07/2023
Accepted: 30/09/2023

rate, were used to measure the disease activity of JIA [9]. According to the Dutch National Healthcare Consensus Committee's criteria for thyroid disorders, hyperthyroidism and hypothyroidism were defined: Overt hypothyroidism was detected by high serum TSH (thyroid stimulating hormone) in addition to a low serum FT4 (free thyroxine) level, subclinical hypothyroidism was detected by high serum TSH with a normal serum FT4 level and hyperthyroidism was detected by low serum TSH levels with high serum FT4 and FT3 (free triiodothyronine). AITD was defined as high levels of TPOA and/or TGA in serum [10].

Methods:

Blood samples were collected in plain sterile tubes and maintained at room temperature for a few minutes, then centrifuged and serum was obtained and kept at -20°C until the time of performing different assays. Measurement of TSH, FT4, and FT3 levels was done using an enzyme-linked immunosorbent assay (ELISA) kit (TSH: Cat. No. DKO013, DiaMetra, Italy; FT3: Cat. No. E1011, CTK Biotech, Inc., USA; and FT4: Cat. No. E1021, CTK Biotech, Inc., USA). The normal ranges for thyroid hormones were as follows: 0.39–3.50 mIU/l for TSH, 1.16–4.34 pg/ml for FT3, and 0.58–2.46 ng/dl for FT4 [11].

By the use of enzyme-linked immunosorbent assays (ELISA), anti-thyroglobulin (TGA) and anti-thyroid peroxidase (TPOA) antibodies were measured (TGA: Cat. No. DKO116, TPOA: Cat. No. DKO115, DiaMetra, Italy). Results were considered elevated (positive test) ≥ 20 AU/ml for TPOA and ≥ 4 AU/ml for TGA and normal (negative test) < 20 AU/ml for TPOA and < 4 AU/ml for TGA. The following labs were recruited from files: CBC (complete blood count), serum creatinine, ALT (alanine transaminase), AST (aspartate transaminase), and ESR (erythrocyte sedimentation rate).

Ethical considerations: The present study received approval from Cairo University's Faculty of Medicine's Research Ethics Committee and was performed in line with the Helsinki Declaration guidelines of 1975. Informed consents were obtained from parents.

Statistical analysis

The statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. Quantitative data were described as mean ± standard deviation or median (range), while qualitative data were described as frequency (percentage). The non-parametric Mann-Whitney test was used to compare quantitative variables, while the Chi square (x^2) test was used to compare categorical data. The Spearman correlation coefficient was used for the correlation between quantitative variables. P values ≤ 0.05 were considered statistically significant.

RESULTS

Demographic and clinical data of the 50 JIA patients showed that the female to male ratio was 0.9: 1, and the age of patients at the time of study ranged from 3 to 16 years old with a median of 9 years old, while the age at diagnosis ranged from 1 to 13 years old with a median of 5.75 years old. Out of the total number of patients, 10 (20%) had consanguineous parents, and 2 (4%) had similar family conditions (Table 1).

Table (1): Demographic data and clinical characteristics of the study group

Variables		**JIA patients (N=50)**
Age (years), mean ±SD		11.5±2.1
Sex, N (%)	**Male**	26 (52.0%)
	Female	24 (48.0%)
Consanguinity, N (%)		10 (20%)
Similar family condition, N (%)		2 (4%)
Age at diagnosis (years), median (range)		5.75 (1 - 13)
Disease duration (years), median (range)		3.00 (0 - 9.5)
Weight (kg), median (range)		26.00 (10.00 - 68.00)
Height (cm), median (range)		121 (80 - 166)
BMI (kg/m2), median (range)		17.05 (10.7 - 36.2)
SBP (mmHg), median (range)		105.00 (93- 120)
DBP (mmHg), median (range)		68.00 (50 - 80)

BMI: body mass index, **SBP:** systolic blood pressure, **DBP:** diastolic blood pressure.

The most prevalent type of JIA in the studied group was systemic JIA (22 patients, 44%), followed by oligoarticular type (15 patients, 30%), and polyarticular type (13 patients, 26%). While, the most frequently recorded JIA symptom in the study group was failure to thrive in 60% of JIA patients, followed by arthritis 46% of patients (Figure 1). Active disease was present in 23 patients (46%) out of 50 patients. Moreover, methotrexate was found to be the most commonly used drug in 82% of patients, as shown in figure (2).

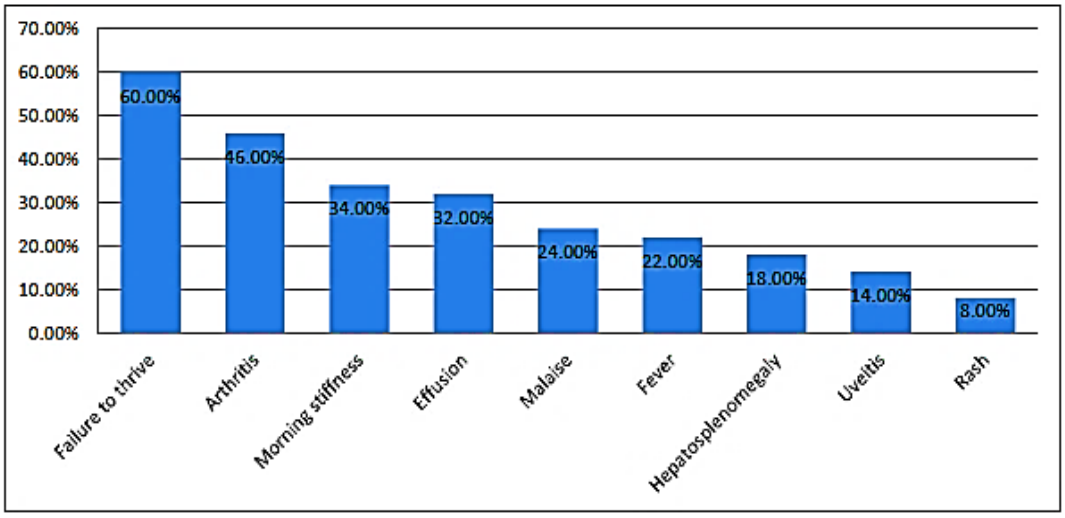

Figure (1): The prevalence of JIA symptoms in the studied patients

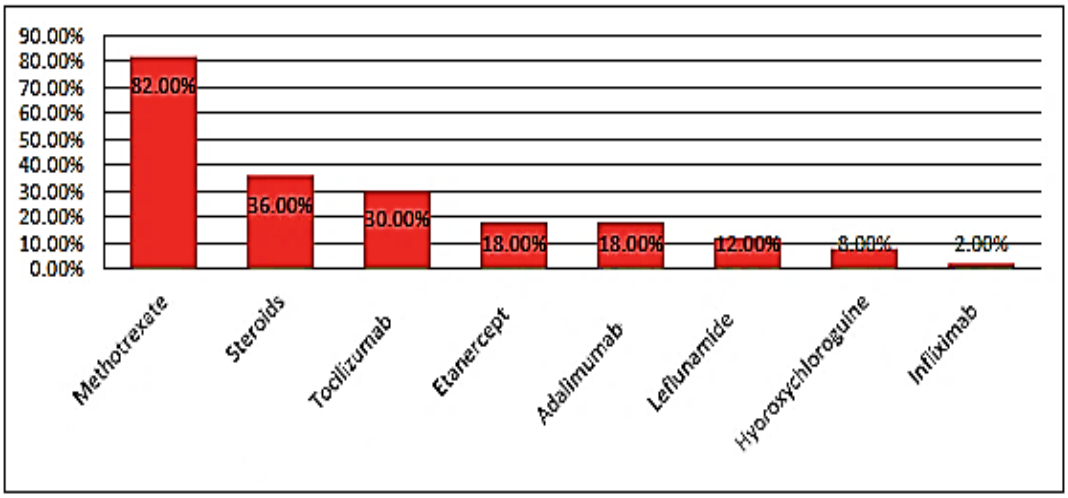

Figure (2): Different types of drugs received by JIA patients.

The results of the laboratory findings of the study group were presented in table (2). Less than half of the JIA patients (48%) were euthyroid, 14 patients (28%) had overt hypothyroidism, 11 (22%) patients had subclinical hypothyroidism, and 1 patient (2%) had subclinical hyperthyroidism as shown in figure (3).

Table (2): Laboratory findings in JIA patients

Variables		**JIA patients (N=50)**
Hemoglobin (g/dl), mean± SD		11.98 ± 1.17
PLT (x 10^3/cmm), mean± SD		361.66 ± 53.11
TLC (x 103/cmm), mean± SD		8.81 ± 2.63
Creatinine (mg/dl), mean± SD		0.42 ± 0.10
AST (U/l), mean± SD		25.74 ± 1.58
ALT (U/l), mean± SD		26.30 ± 5.88
FT3 (pg/mL), mean± SD		1.94 ± 0.4
FT4 (ng/dL), mean± SD		0.62 ± 0.1
TSH (µIU/mL), mean± SD		2.55 ± 0.22
Anti-TG, N (%)	**Normal (< 4 AU/ml)**	50 (100.0%)
	Elevated (≥ 4 AU/ml)	0 (0.0%)
Anti-TPO. N (%)	**Normal (< 20 AU/ml)**	50 (100.0%)
	Elevated (≥ 20 AU/ml)	0 (0.0%)

Anti-TPO: anti-thyroid peroxidase, **Anti-TG:** anti-thyroglobulin, **TSH:** thyroid stimulating hormone, **FT3:** free triiodothyronine, **FT4:** free thyroxine.

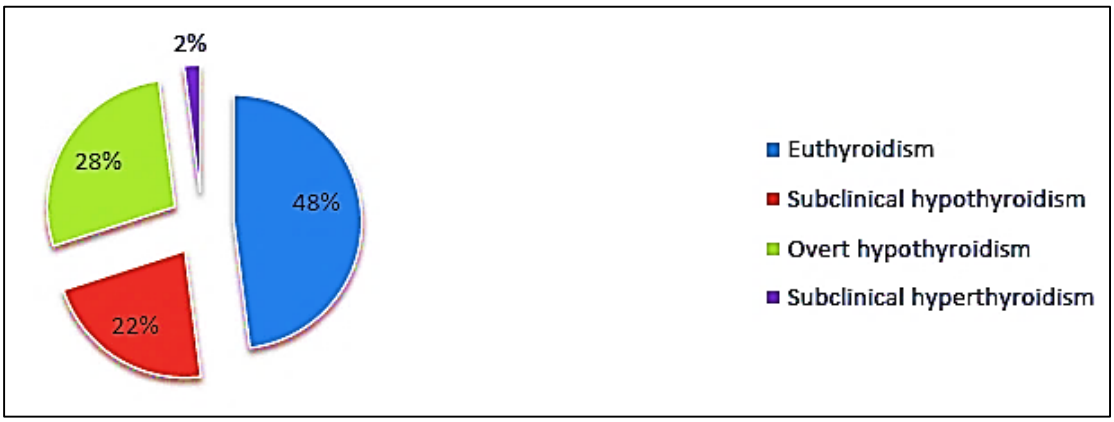

Figure 3: Frequency of different Thyroid states among JIA cases

The distribution of different thyroid disorders among different types of JIA in the study group was represented in table (3) and showed that subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism were detected more commonly in JIA patients with systemic-onset. While, normal thyroid function (euthyroidism) was detected more in polyarticular type. No statistically significant relationship was found between disease activity and thyroid function tests (Table 4).

Table (3): Frequency of different Thyroid states among different JIA types

	Subclinical hypothyroid N=11 (22%)	Overt hypothyroid N=14 (28%)	Hyperthyroid N=1 (2%)	Euthyroid N=24 (48%)	Total no of patients N=50
Systemic JIA	7	7	1	7	22 (44%)
Oligoarticular JIA	3	5	0	7	15 (30%)
Polyarticular JIA	1	2	0	10	13 (26%)

Data presented as number (percentage)

Tables (4): The relation between thyroid function tests and JIA activity

	JIA Activity		P value
	Active	Inactive	
FT3 (Pg/ml), mean± SD	1.91 ± 0.18	1.97 ± 0.1	0.830
FT4 (ng/dl), mean± SD	0.60 ± 0.15	0.63 ± 0.13	0.938
TSH (µIU/l), mean± SD	2.46 ± 0.88	2.63 ± 0.46	0.733

On testing correlations between thyroid function labs and patients' data, there were significant negative correlations between free T4 and weight, body mass index, and height. Also, a significant negative correlation was shown between FT3 and disease duration. Moreover, a positive correlation was shown between FT3 and age at diagnosis of JIA (Table 5).

Table 5: Correlations between thyroid function tests and patients' data

		FT3 pg/ml	FT4 ng/dl	TSH mIU/l
Current age of patient	**Correlation coefficient**	0.05	-0.15	0.22
	P value	0.71	0.31	0.13
WT (kg)	**Correlation coefficient**	-0.034	-0.350	0.216
	P value	0.81	0.01*	0.13
HT (cm)	**Correlation coefficient**	-0.06	-0.30	0.20
	P value	0.68	0.03*	0.17
BMI (kg/m^2)	**Correlation coefficient**	0.01	-0.29	0.07
	P value	0.96	0.04*	0.65
Age at Diagnosis (years)	**Correlation coefficient**	0.31	-0.02	0.18
	P value	0.03*	0.88	0.21
Disease duration (years)	**Correlation coefficient**	-0.38	-0.06	0.08
	P value	0.01*	0.67	0.58
Number of Joints	**Correlation coefficient**	-0.03	0.07	0.03
	P value	0.85	0.65	0.86

*P value < 0.05 is considered statistically significant **BMI:** body mass index, **WT:** weight, **HT:** height.

DISCUSSION

The present study revealed that thyroid disorders were found in 52% of JIA patients and the most prevalent thyroid abnormality was overt hypothyroidism in 28% of patients, followed by subclinical hypothyroidism in 22% of patients and subclinical hyperthyroidism in 1 patient (2%). Similarly, **Robazzi *et al.*** [12] found that among patients with JIA, 40% of cases had thyroid disorders, including subclinical hypothyroidism (13% of cases). Moreover, many studies found that clinical hypothyroidism was the most prevalent thyroid abnormality accompanying rheumatoid arthritis (RA) [13–16]. On the other hand, **Stagi *et al.*** [17] found that 14 out of 151 patients (9%) had subclinical hypothyroidism. Common causes of hypothyroidism in RA have been studied, including the use of corticosteroids or salicylates to treat RA, which have been found to affect the function of thyroid gland [18, 19].

In the present study, active JIA was present in 23 patients (46%) out of 50 patients. No statistically significant association was detected between disease activity and thyroid function tests. Likewise, some former studies could not establish a link between RA disease activity and hypothyroidism and came to the conclusion that thyroid hormonal abnormalities were associated with the duration of the disease rather than the disease activity [19-20].

In this study, subclinical hypothyroidism, overt hypothyroidism, and hyperthyroidism were detected more often in JIA patients with systemic-onset than in those with polyarticular or oligoarticular onset, while the euthyroidism was detected more frequently in JIA patients with polyarticular type. This contradicts the finding of **Stagi *et al.*** [17] who found that subclinical hypothyroidism was more commonly identified in patients with oligoarticular onset when compared to those with polyarticular or systemic onset.

Only a few studies have investigated the link between autoimmune thyroiditis, and JIA and according to their reports, anti-thyroid antibodies were prevalent in JIA patients [21, 22]. This study could not demonstrate the existence of anti-thyroid antibodies in JIA patients. In this study, thyroid autoantibodies (TPOA and TGA) were negative among JIA patients, which suggest a low prevalence of positive antibodies in JIA patients. This is similar to **Stagi *et al.*** [17] who stated that none of the JIA patients with oligoarticular type had positive thyroid antibodies. However, six patients (4%) showed positive TPOA, five showed positive TGA, and six were positive for both. Moreover, **Harel *et al.*** [21] found that 7 out of 62 JIA patients (11.3%) were positive for TGA, while 5 out of 65 (7.9%) JIA patients were positive for TPOA. Additionally, **Unsal *et al.*** [23] detected anti-thyroid antibodies in only 4 JIA patients out of 80 (5%) and stated that no significant variance were found between the patients and control groups concerning the presence of anti-thyroid antibodies ($p = 0.17$). Also, **Tronconi *et al.*** [6] found that 8 JIA patients (10.1%) had autoimmune thyroid disease (AITD). On the other hand, **Robazzi *et al.*** [12] reported a significant prevalence of autoimmune thyroid disorders in patients with JIA, suggesting that routine screening for thyroid diseases in this group must be considered. The ethnic and environmental variations in the studied populations could explain the differences in the percentage of anti-thyroid antibodies [13].

Concerning JIA types, systemic JIA was diagnosed in 44%, while oligo-articular in 30% and poly-articular in 26% of patients. This comes in agreement with **Al-Hemairi *et al.*** [24] and **Bahabri *et al.*** [25]. Conversely, **Abdwani *et al.*** [26] reported that the most common JIA subtype was polyarticular rheumatoid factor negative (39.2%) then oligoarthritis (31.8%), systemic (17.8%), and polyarticular rheumatoid factor positive (7.5%). Moreover, **Harrold *et al.*** [27] and **Thierry *et al.*** [28] stated that oligoarthritis was the most frequent form. This variance in the predominant JIA subtype can be explained by the fact that relative frequencies of different JIA subtypes vary in different areas of the world. For example, oligoarticular JIA is more prevalent in Scandinavia, and enthesitis-related JIA is prevalent in Latin America [29].

In the present study, 26 out of 50 JIA patients (52%) were males and 24 patients (48%) were females, with a male to female ratio of 1.08: 1. This comes in agreement with **Unsal *et al.*** [23] and **Özdoğan *et al.*** [30] who found a predominance of males among JIA patients. On the contrary, many studies reported a higher incidence of JIA in females than males [31, 32]. This was explained by **Thierry et al.** [28] who concluded that incidence and prevalence vary greatly most probably due to methodological issues, classification used, and time of diagnosis.

In the current study, failure to thrive and arthritis were the most frequent symptoms present in 60% and 46% of patients respectively, followed by morning stiffness, effusion, malaise, fever, hepatosplenomegaly, uveitis, and rash (34%, 32%, 24%, 22%, 18%, 14%, and 8% respectively). In agreement with our study, some studies stated that JIA can be associated with growth retardation due to pro-inflammatory cytokines such as IL-6, long-term corticosteroid therapy, malnutrition, and stress (linked to having a chronic illness or disability) [33, 34]. In the study done by **Sen *et al.*** [32], the most prevalent early-presenting symptoms were arthralgia in 98.1%, fever in 52.1%, fatigue in 39.9%, malaise in 53.5%, and morning stiffness in 15.5%. However, this contradicts **Al-Hemairi *et al.*** [24] who reported that fever was present in 41.46% of JIA patients.

Regarding the treatment of JIA patients in this study, methotrexate was the most frequently used treatment in 82% of patients. Similarly, **Berthold *et al.*** stated that the

most often used disease-modifying anti-rheumatic medication (DMARD) prescribed was methotrexate (60.6%) [35]. On the contrary, **Abdwani *et al.*** [26] reported that non-steroidal anti-inflammatory drugs (NSAIDs) were the most used drugs in 97% of patients, followed by steroids, methotrexate, and biologic agents in 74%, 61%, and 34% respectively. Also, **Sen *et al.*** [32] reported that NSAIDs were the most frequently used drugs (89.2%), followed by methotrexate (71.4%) and steroids (37.6%).

Limitations: Due to financial limitations, we only included a relatively small number of participants in our study. To illustrate the prevalence of autoimmune thyroiditis in JIA patients, additional research involving a larger patient population is required.

CONCLUSIONS

To reduce the risk of delayed or undiagnosed thyroid diseases, it is necessary to routinely screen for thyroid function abnormalities in children with juvenile idiopathic arthritis.

ABBREVIATIONS

AITD: Autoimmune thyroid disease.
ALT: alanine transaminase **AST:** aspartate transaminase
CBC: complete blood count **ELISA:** enzyme-linked immunosorbent assay **ESR:** erythrocyte sedimentation rate **FT3:** free triiodothyronine **FT4:** free thyroxine **JIA:** juvenile idiopathic arthritis,
JRA: Juvenile Rheumatoid Arthritis
NSAID: non-steroidal anti-inflammatory drugs **RA:** rheumatoid arthritis **SPSS:** statistical package for the Social Sciences **TGA:** Anti-thyroglobulin antibodies
TPOA: Anti-thyroid peroxidase antibodies.
TSH: Thyroid stimulating hormone.

Funding: Not applicable.
Competing of interests: The authors declare that they have no competing interests.

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